Type 2 immunity in tissue repair and fibrosis

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Abstract | Type 2 immunity is characterized by the production of IL-4, IL-5, IL-9 and IL-13, and this immune response is commonly observed in tissues during allergic inflammation or infection with helminth parasites. However, many of the key cell types associated with type 2 immune responses — including T helper 2 cells, eosinophils, mast cells, basophils, type 2 innate lymphoid cells and IL-4- and IL-13-activated macrophages — also regulate tissue repair following injury. Indeed, these cell populations engage in crucial protective activity by reducing tissue inflammation and activating important tissue-regenerative mechanisms. Nevertheless, when type 2 cytokine-mediated repair processes become chronic, over-exuberant or dysregulated, they can also contribute to the development of pathological fibrosis in many different organ systems. In this Review, we discuss the mechanisms by which type 2 immunity contributes to tissue regeneration and fibrosis following injury.

Type 2 immunity is characterized by increased production of the cytokines IL-4, IL-5, IL-9 and IL-13 (REF. 1). The T helper 1 (T_H1) and T_H2 paradigm was first described approximately three decades ago[2], and for many of the intervening years, type 2 immunity was largely considered as a simple counter-regulatory mechanism controlling type 1 immunity[3] (BOX 1). Early studies showed that when components of the type 2 response were ablated, susceptibility to a variety of autoimmune diseases generally increased due to dysregulated type 1-driven inflammation. Today, our understanding of the diverse roles of type 2 cytokines in host immunity and inflammatory disease is becoming clearer, with type 2 immunity exhibiting either host-protective or pathogenic activity depending on the specific setting[4]. In addition to suppressing type 1- and T_H17-driven inflammation, type 2 immunity is directly involved in tissue repair and regeneration following injury, with many studies suggesting critical roles for IL-4- and IL-13-activated macrophages in the resolution of inflammation and restoration of tissue homeostasis[5,6]. The specific mechanisms regulating tissue repair by macrophages activated by type 2 cytokines and other cell types that characterize type 2 inflammation, including eosinophils, mast cells, basophils, T_H2 cells and group 2 innate lymphocytes (ILC2s), remain ill defined. Moreover, while type 2 immunity helps to restore tissue homeostasis following injury, type 2 immune responses can also lead to the development of pathological fibrosis[7] (FIG. 1). The mechanisms that transform these tissue-regenerative type 2 responses into progressive fibrotic disorders remain unclear, although persistent activation of tissue repair pathways is a major contributing mechanism in most cases. In this Review, we provide a brief overview of fibrotic diseases that have been linked to activation of type 2 immunity, discuss the various mechanisms that contribute to the initiation and maintenance of type 2 inflammation and examine the ways in which these pathways may become chronically activated or dysregulated. We highlight the key cell types that regulate type 2-dependent repair and fibrosis responses and illustrate both the mechanisms through which type 2 cytokines interact with other key mediators to instruct tissue repair and how these pathways contribute to the development of fibrosis when dysregulated.

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doi:10.1038/nri.2017.90
Published online 30 Aug 2017

Diseases involving type 2 fibrosis

Type 2 fibrosis in the liver. The liver is a key detoxifying organ that is frequently impacted by infections, injuries and insults that can lead to fibrosis over time. Chronic helminth infections evoke highly polarized type 2 immune responses that are often associated with fibroproliferative lesions, particularly during the chronic stages of infection[4,8]. The genus *Schistosoma* contains several species of trematode flatworms that currently infect over 200 million individuals worldwide[9]. These worms lay eggs in the vasculature, and these eggs become lodged in the small venules of the liver, lung, gut and bladder, causing chronic irritation, granulomatous inflammation and fibrosis[9]. The fibrotic pathology that defines severe schistosomiasis has been well characterized and is largely influenced by the T_H2-associated

Box 1 | **Type 1 and Type 2 paradigm**

In this Review, type 1 immunity is defined by the activity of T helper 1 cells, type 1 innate lymphoid cells, neutrophils and classically activated macrophages. Type 1 immunity is critical for defence against many intracellular pathogens, bacteria, viruses and other microorganisms. By contrast, type 2 immunity promotes immunity against extracellular parasites and helminths, helps to maintain metabolic homeostasis and regulates tissue repair following injury. Type 2 immunity is characterized by the cytokines IL-4, IL-5, IL-9, IL-13, IL-25, IL-33 and thymic stromal lymphopoietin and associated cell types, including eosinophils, mast cells, basophils, T helper 2 cells, group 2 innate lymphoid cells and IL-4- and IL-13-activated macrophages. Many studies have shown that type 1 and type 2 immune responses display substantial cross-regulation. Therefore, therapeutic strategies that target just one arm of the immune response often lead to marked increases in the opposing response.

cytokines IL-4, IL-5 and IL-13 and associated accessory cells, including eosinophils and IL-4- and IL-13-induced alternatively activated macrophages[10,11].

Closely related are liver flukes, including the species *Clonorchis sinensis* and *Opisthorchis viverrini*, which currently affect over 50 million individuals worldwide owing to consumption of undercooked freshwater fish[12]. These worms, which reside in the large branching bile ducts, feed both on the cholangiocytes lining the bile ducts and on bile itself, causing extreme biliary hyperplasia that often progresses to cholangiocarcinoma[13,14]. Liver flukes induce IL-4, IL-5 and IL-13 responses[15–17], and it has been suggested that the fibrosis associated with liver fluke infection is IL-13-dependent[16,17].

In addition to parasites, the development of type 2 cytokine-driven fibrosis has been linked to several other pathogens and hereditary diseases. Subsets of patients with hepatitis C virus infection, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, biliary atresia and non-alcoholic steatohepatitis (NASH) exhibit significantly increased levels of IL-4, IL-5 and/or IL-13 in addition to many type 1- and T_H17 cell-associated cytokines[18,19]. However, the specific contributions of these cytokines in these diseases remain less clear.

Type 2 fibrosis in the lung. Like the liver, which has the capacity to regenerate from as little as 25% of its original mass[20], the lung is remarkably resilient following injury and exhibits substantial reparative ability[21]. Nevertheless, in response to chronic injury and insults, the wound healing pathways can become overactive and dysregulated, resulting in poor regenerative potential along with increasing fibrosis. For these reasons, pulmonary diseases, including asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), are very common. These diseases affect hundreds of millions of people globally and represent some of the leading causes of chronic morbidity and mortality[22,23]. Restoration of the normal architecture of the lung following injury requires a rapid and controlled repair process, which, if uncoordinated, can result in local scarring, with fibrotic lesions forming in what is otherwise a highly elastic and flexible organ. This dysregulated repair of pulmonary tissue following infection or insults from environmental triggers can predispose individuals to subsequent infections[24] and cause lung dysfunction[25]. Thus, pulmonary fibrosis is of significant medical concern, and there are very few effective treatment options. Although it is difficult to distinguish cause from consequence, pulmonary fibrosis has been observed in an array of pulmonary diseases, including acute respiratory distress syndrome[26], asbestosis[27], asthma[28], bacterial infection[29], bronchiolitis[30], COPD[31], cystic fibrosis[32], emphysema[33], lung cancer[34], pneumonia[35], IPF and sarcoidosis[36].

Whether common mechanistic pathways among these diseases contribute to dysregulated wound healing and fibrotic scaring is not clear. Two prevailing upstream cytokine-driven inflammatory pathways in the lung have been identified, involving transforming growth factor β (TGFβ) and/or IL-13 (REF. 37). Several years ago, we and others identified that activation of an IL-1–IL-17A-associated axis can propagate a TGFβ-dependent pulmonary fibrogenic pathway[38–40]. Although elevated levels of IL-17A and excessive activation of IL-17A-dependent pathways contribute to the inflammatory milieu in many of the above-mentioned pulmonary diseases[41–47], it is currently unclear whether IL-17A directly contributes to the development of pulmonary fibrosis. Type 2 cytokines, and specifically IL-4 and IL-13, are elevated in many of these pulmonary diseases[48–57], with IL-13 attracting substantial attention as a therapeutic target for asthma[58]. Promising data from preclinical studies led to the development of several clinical trials targeting IL-13. In particular, two humanized anti-IL-13 monoclonal antibodies (tralokinumab[59] and lebrikizumab[60]) and an anti-IL-4Rα monoclonal antibody (dupilumab[61]) have been tested in patients with mild-to-moderate or severe asthma and were found to reduce the frequency of asthma exacerbations and to improve lung function in some, but not all, studies. For example, despite encouraging preclinical data, tralokinumab recently failed to meet its primary end point of reducing the annual exacerbation rate in the first of two phase III trials in severe uncontrolled asthma. Although lebrikizumab showed mixed results in asthma, clinical studies in COPD, atopic dermatitis and IPF are ongoing. Unfortunately, airway remodelling and fibrosis severity were not reported in the asthma trials. Increased innate and adaptive immune cell-derived IL-13 and elevated expression of IL-13Rα1 and IL-13Rα2 have been observed in patients with IPF[62–65], further supporting the hypothesis that IL-13 contributes to pulmonary fibrosis. Indeed, using a humanized severe combined immunodeficiency (SCID) mouse model of IPF, in which mice are infused with fibroblasts from patients with IPF, Murray and colleagues observed a significant reduction in fibrosis and increased repair of the airway epithelium following anti-IL-13 (tralokinumab) treatment[66]. In relation to IL-13-driven pulmonary fibrosis, both TGFβ-dependent[67,68] and TGFβ-independent[37] mechanisms have been proposed; however, it remains unclear whether therapeutically targeting IL-13 or any of the TGFβ family members would provide a clinical benefit in fibroproliferative diseases of the lung and to what degree IL-17A and TGFβ interact with type 2 immunity in various aetiologies of pulmonary fibrosis.

Alternatively activated macrophages
These non-classically activated macrophages consist of several functionally and transcriptionally distinct macrophage subsets with roles in wound repair, fibrogenesis and dampening of the inflammatory response, among others. These cells are sometimes referred to as 'M2' macrophages; however, by convention, it is best to include the activating stimulus in the description, such as 'IL-4-activated macrophages'.

Cholangiocarcinoma
A cancer of the bile duct epithelium that is relatively rare in the Western world but more common in areas endemic for liver flukes.

Primary sclerosing cholangitis
An idiopathic disorder resulting in chronic inflammation of the bile ducts that progresses to ductal narrowing and eventual ductal loss, followed by replacement with fibrotic tissue.

Biliary atresia
A disease characterized by the progressive loss of bile ducts usually in early childhood. Although the cause of biliary atresia is debated, there is evidence to suggest an autoimmune component to the disease that is precipitated by infection or the passage of maternal toxins across the placental barrier.

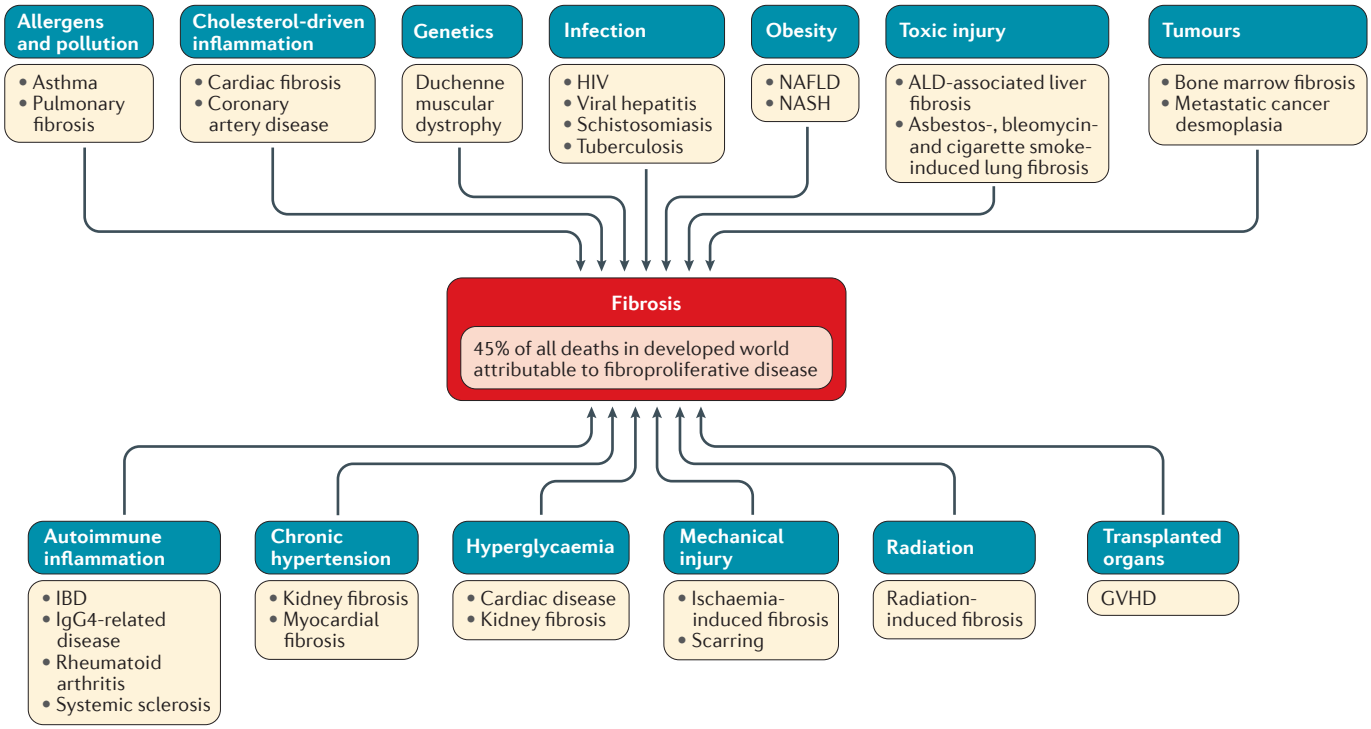

Figure 1 | **Major causes of fibrosis and associated diseases.** Fibrosis is a common final outcome of most chronic inflammatory diseases, and it can impact organ function and ultimately lead to organ failure and death. As many as 45% of all deaths in the developed world are believed to be attributable to pathological tissue remodelling. In the figure, triggers of fibrosis are represented in blue boxes, and the associated diseases are shown in the cream-coloured boxes. ALD, alcoholic liver disease; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Type 2 fibrosis in other organs. Type 2 fibrosis can affect nearly every organ in the body; however, due to space limitations, we will focus mainly on examples from the liver and lung. Nevertheless, there are a few other noteworthy examples that will be highlighted. IgG4-related disease is a chronic inflammatory disease characterized by high levels of infiltrating IgG4-secreting plasma cells. This disease has distinct manifestations that can affect disparate organs; however, several commonalities have emerged over the past few years, including infiltration of eosinophils and progression to fibrosis[69], perhaps suggesting a role for type 2 immunity in disease pathogenesis. The anti-CD20 antibody rituximab, which depletes B cells, has shown some efficacy in patients with IgG4-related disease[70]; nevertheless, additional mechanistic work is needed to determine the role of B cells and IgG4 relative to other cell types, including T_H2 cells and eosinophils, and whether they contribute to the development of fibrosis in this disease.

Atopic dermatitis is a disease in which the accumulation of mast cells and eosinophils within the skin drives chronic pruritus and thickening of the skin, resulting in a significant loss of quality of life for patients[71]. Recent studies have identified the alarmins IL-25 and IL-33 as well as ILC2s as key drivers of atopic dermatitis[72,73]. Furthermore, in clinical trials using dupilumab, a humanized monoclonal antibody that blocks both IL-4 and IL-13 signalling, 85% of patients receiving the antibody met the primary end point of a 50% decrease in the eczema area and severity score, compared with only 35% of patients in the placebo arm[74].

Another noteworthy disease, ulcerative colitis, is a chronic inflammatory bowel disease that results in severe epithelial damage and ulceration of the large intestine[75]. The cytokine response observed in ulcerative colitis is complex[76]; however, elevation of type 2 cytokines has been noted in the lamina propria of the gut in animal models of ulcerative colitis and in patients with active disease, suggesting that blockade of these cytokines may be efficacious[77,78]. Nevertheless, two clinical trials in which IL-13 was blocked (using tralokinumab[79] or anrukinzumab[80]) in ulcerative colitis failed to meet their primary end points. Surprisingly, patients receiving higher doses of anrukinzumab fared worse than those receiving lower doses[80]. It is interesting to speculate that blocking type 2 immunity in diseases with mixed cytokine responses, such as ulcerative colitis, may dysregulate important regulatory pathways that keep type 1- and T_H17-driven inflammation in check. Cross-regulation between type 1 and type 2 immunity, particularly during therapeutic interventions, is a key focus of this Review and will be discussed in greater detail below.

Initiation of type 2-driven fibrosis

Role of alarmins in the type 2 response and fibrosis. Mucosal epithelial cells of the airways and intestine both provide physical barriers to the environment and possess

Steatohepatitis
This term refers to liver inflammation that accompanies fat accumulation in the liver, typically as a result of chronic alcohol consumption or obesity.

Alarmins
Predominantly epithelial- and stromal-derived cytokines that are produced by damaged or stressed cells as an 'alarm' signal. The canonical alarmins consist of IL-25, IL-33 and thymic stromal lymphopoietin and are able to induce and potentiate aspects of both the innate and the adaptive type 2 responses.

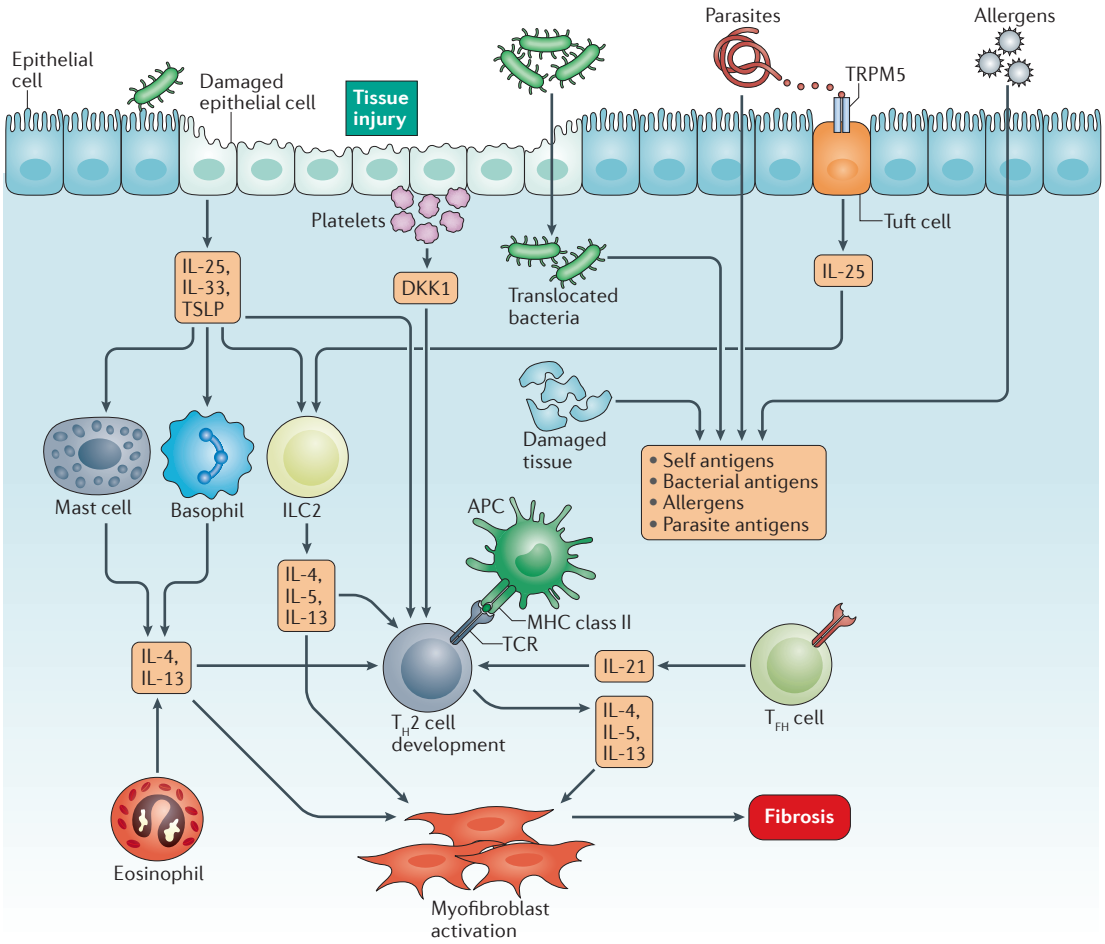

Figure 2 | **Initiation of type 2 immune responses.** Following tissue injury, damaged epithelial cells secrete IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). These alarmins signal through innate cells, including basophils, mast cells and group 2 innate lymphoid cells (ILC2s), resulting in the production of the type 2 cytokines IL-4, IL-5 and IL-13. These cytokines support naive $CD4^+$ T cell differentiation into T helper 2 (T_H2) cells and support T_H2 cell effector functions. Dickkopf-related protein 1 (DKK1) secreted from platelets at the site of injury can similarly support the differentiation of T_H2 cells. Bacterial translocation and self-antigens that are exposed at the site of tissue injury as well as antigens from allergens and parasites can be presented to T cells by antigen-presenting cells (APCs). Additionally, parasite antigens can be detected by specialized epithelial cells, known as tuft cells, through chemo-sensing receptors such as transient receptor potential cation channel subfamily M member 5 (TRPM5) and gustducin (not depicted), resulting in IL-25 release, which subsequently activates ILC2s. IL-21 produced by follicular helper T (T_{FH}) cells and IL-4 and IL-13 released by eosinophils can augment these processes. IL-4 and IL-13 secreted from basophils, mast cells, eosinophils and ILC2s also directly contribute to the activation of myofibroblasts and the development of fibrosis. TCR, T cell receptor.

Tuft cells
A very rare chemo-sensing epithelial cell type that is spread throughout the gastrointestinal and respiratory tracts. Tuft cells secrete the alarmin IL-25 in response to parasitic infections and perhaps other stimuli and are thought to be important sentinels for and innate initiators of the type 2 response.

Goblet cells
A specialized, mucus-secreting epithelial cell found throughout the gastrointestinal and respiratory tracts and across mucosal surfaces. Goblet cells and their secreted mucins are critical for protecting mucosal surfaces, maintaining barrier integrity and removing large extracellular irritants and debris.

instructive properties to guide immune responses[81,82]. Recent studies have identified a variety of epithelial cells, including IL-25-secreting tuft cells[83–85], antigen-sensing goblet cells[86] and phagocytic epithelial cells[87], suggesting a greater division of labour among the specialized cells of the mucosal epithelium than previously appreciated. Originally identified as a T cell-derived cytokine[88,89], IL-25 can initiate a type 2 cytokine cascade involving the induction of IL-4, IL-5 and IL-13. Several years after the initial identification of IL-25, epithelial expression of *ACT1* (which encodes TRAF3 interacting protein 2 and is also known as *TRAF3IP2*) was shown to potentiate IL-25 signalling through a non-lymphocyte, non-natural killer (NK) cell, non-granulocyte lineage, which we now know as ILC2s[90]. Around the same time, it was observed that epithelial cell-derived thymic stromal lymphopoietin (TSLP) activated local dendritic cells (DCs) to secrete CC chemokine ligand 22 (CCL22) and CCL17, promoting T_H2 cell differentiation and propagating type 2 allergic inflammation. A third member of the alarmins, IL-33, was also identified as a T_H2 cell-promoting cytokine[91] that signals through IL-1 receptor-like 1 (IL1RL1; also known as protein ST2) on mast cells and T_H2 cells; however, it has since been shown that IL-33 also has important T cell-independent immune functions[92–94].

Alarmins are considered to be some of the earliest of the type 2 cytokines to be secreted following tissue damage, and they have the capacity to both initiate and propagate a fulminant type 2 immune response (FIG. 2). If left unchecked, the alarmins can also contribute to the initiation and progression of fibrosis, with indirect

actions via innate or adaptive immune cells. For example, both IL-13-secreting ILC2s and IL-25 have been observed in patients with IPF, leading Hams and colleagues[95] to examine the role of IL-25 in the development of IPF. Indeed, using *Schistosoma mansoni* eggs, they showed that IL-25-activated ILC2s exhibited substantial production of the pro-fibrotic cytokine IL-13, indicating that this innate axis may contribute to human pulmonary fibrosis. Similarly, intranasal delivery of recombinant IL-25 in mice led to airway inflammation, connective tissue growth factor (CTGF) and TGFβ1 production and pulmonary fibrosis[96]. Similar observations have been made for IL-33, with elevated levels of IL-33 detected in dermal tissues during cutaneous fibrosis[97,98], in the lung or intestinal epithelium of patients with pulmonary fibrosis or fibrotic colitis[99–102] and in the liver of mice with hepatic fibrosis[99]. Mechanistically, it has been proposed that IL-33 drives fibrosis by inducing IL-13 production by ILC2s, macrophages[103] and eosinophils[100]. TSLP has also been observed in human and experimental pulmonary fibrosis[104,105], systemic sclerosis[106–108], colonic fibrosis[109] and skin fibrosis[110]. Gain-of-function and loss-of-function experiments indicate that TSLP has pro-fibrotic properties, triggering mitogen-activated protein kinase signalling pathways in fibroblasts, which leads to the synthesis of collagens[111–113]. Disruption of TSLP receptor signalling also reduced IL-13-driven[110] and TGFβ-driven[108] fibrosis, suggesting that TSLP can also operate downstream of IL-13 and TGFβ; however, these results need to be verified. Additionally, there is some evidence suggesting that epithelial-derived IL-1α may be an upstream initiator of IL-33 and TSLP and that disruption of IL-1α signalling may prevent allergic priming by preventing DC migration[114].

Given the overlapping expression and the possible context-dependent function of the alarmins, we investigated the potential redundancy between the alarmins by inhibiting IL-25, IL-33 and TSLP individually or collectively following the initiation of allergen-induced airway inflammation, chronic *S. mansoni*-driven hepatic fibrosis or acute pulmonary fibrosis in mice[115]. Blockade of IL-25, IL-33 or TSLP had no impact on IL-13-mediated chronic hepatic or acute pulmonary fibrosis; however, blockade of all three alarmins significantly reduced inflammation, ILC2 recruitment, eosinophilia and fibrosis[115]. During chronic house dust mite (HDM)-driven airway inflammation, ablation of all three alarmins had no impact on established disease; however, blockade during the priming phase prevented the establishment of inflammation and the progression of airway pathology, suggesting that combined therapeutic intervention may be required to temper type 2-driven fibrosis in some settings.

Role of adaptive T_H2 cell responses in fibrosis. The activation of innate immune cells, including basophils[116] and ILC2s[117], contributes to the local and early secretion of IL-4, IL-5 and IL-13. Following T cell receptor (TCR) engagement and co-stimulation, IL-4 receptor signalling via signal transducer and activator of transcription 6 (STAT6) and GATA3 in T cells instructs a T_H2 cell differentiation programme[118] (FIG. 2). More than 20 years ago, Cheever and colleagues identified an important role for IL-4 and T_H2 cells in the development of *S. mansoni*- and *S. japonicum*-associated hepatic fibrosis[119,120]. In these cases, IL-13 was continuously secreted by T_H2 cells specific for parasite antigen, and this orchestrated a fibrotic response around tissue-trapped parasite eggs[121]. Similarly, fungal- and viral-associated pulmonary fibrosis[122,123], in addition to post-irradiation[124] and silica-induced pulmonary fibrosis, have been associated with the accumulation of T_H2 cells. T_H2 cell-associated fibrosis is not restricted to the lung and liver; experimental renal fibrosis[125,126], soft-tissue fibrosis[127] and peritoneal fibrosis[128] have also been associated with the accumulation of T_H2 cells.

The antigen specificity of T_H2 cells in many of these settings is unclear. Bacteria-specific T_H2 cells have been reported[129,130]; however, it is unclear whether local microorganisms contribute to T_H2 cell activation and accumulation at fibrotic sites. It has also been suggested that self-antigens that are exposed following local tissue damage could promote the activation of T_H2 cells at damaged tissue sites[131]; however, this needs to be clarified. Alternatively, recent studies have shown that T_H2 cells can produce IL-13 in direct response to alarmins, allowing these cells to adopt innate-like properties in response to tissue-derived cytokines[132–134].

In addition to IL-4, a recent study identified platelet-derived Dickkopf-related protein 1 (DKK1), a Wnt antagonist, as an important contributor to T_H2 cell differentiation *in vitro* in combination with TCR engagement and during T_H2 cell-mediated airway allergy and immunity[135]. This study provides physiological and mechanistic links among local tissue damage, platelet activation and T_H2 cell differentiation in addition to the well-established role of platelets as a key source of platelet-derived growth factor (PDGF). Whether additional tissue-derived signals contribute to T_H2 cell differentiation following local tissue damage is unclear. More detailed experimental analysis of the TCR repertoire of T_H2 cells at fibrotic sites is required to determine the antigen specificity of T_H2 cells and potential pathogenic stimuli. Nevertheless, as they have the capacity to secrete both inflammatory- and regulatory-type cytokines and chemokines[136], T_H2 cells can recruit and activate innate and adaptive immune cells that are involved in both initiating and resolving inflammation.

It has long been appreciated that T_H2 cell-derived IL-4 and IL-13 can alternatively activate macrophages[137]. We showed that a follicular helper T (T_{FH}) cell-associated cytokine, IL-21, could accentuate the effects of IL-4 and IL-13 on macrophages by upregulating their expression of IL-4Rα and IL-13Rα1 (REF. 138). IL-21R-deficient mice showed a significant reduction in T_H2 cell-mediated fibrosis and immunity following *S. mansoni* or *Nippostrongylus brasiliensis* infection[138] supporting a critical role for IL-21 in amplifying T_H2 cell-mediated pathologies. These observations were supported by Coquet and colleagues[139], who identified allergen-specific, tissue-associated IL-21-secreting T cells that were distinct from T_H2, T_H17 and T_{FH} cells. Similar to our observations, these

authors found that IL-21R-deficient mice developed reduced allergen-driven airway inflammation. In addition to the inflammatory role of T_H2 cells, T_H2 cell-derived cytokines can stimulate local fibroblasts, endothelial cells and epithelial cells, extending their influence beyond the immune system[140], as we describe in more detail below.

Role of metabolism in type 2 responses. Local and systemic energy resources influence all physiological responses, including normal organ function, tissue regeneration and repair. Close relationships among metabolism, adipose tissue dysfunction, type 2 immunity and fibrosis[141] are slowly being revealed. The immune system is particularly sensitive to metabolite availability, and several recent studies have highlighted a two-way interaction between type 2 immune responses and metabolic programmes. For example, the differentiation of T_H2 cells from quiescent naive T cells requires mammalian target of rapamycin complex 1 (mTORC1)-dependent and regulatory-associated protein of mTOR (RAPTOR)-dependent metabolic reprogramming, which increases glycolysis and glucose metabolism[142]. By contrast, alternative activation of macrophages by IL-4 and IL-13 requires tumour progression locus 2-dependent lipid oxidative metabolism[143,144] to both regulate T_H2 cell proliferation and limit fibrotic responses[144,145]. In return, type 2 immune responses also influence adipocyte metabolism, providing a feedback loop between metabolic and immune responses. Specifically, ILC2-derived IL-5 and IL-13 and eosinophil-derived IL-4 regulate adipocyte development, beige adipogenesis and caloric expenditure[143,146–148]. The interactions between type 2 immunity and metabolism[149] and the metabolic requirements of fibrosis[150–152] have been extensively reviewed elsewhere[153]. However, it is interesting to speculate that targeting the metabolic requirements of type 2 immunity may starve type 2 immune responses and slow the progression of type 2-dependent fibrosis[154].

Cell-specific roles in type 2 fibrosis

Role of monocytes and macrophages. Monocytes and macrophages are crucial regulators of the initiation, maintenance and resolution of repair following injury and dictate whether wounds regenerate successfully or progress to pathological fibrosis. To achieve these disparate functions, monocytes and macrophages undergo major phenotypic, functional and metabolic changes in response to signals found in the local milieu, which result in substantial functional changes in the surrounding cells and extracellular matrix[7,155,156]. These factors prove critical in determining whether the microenvironment favours ongoing inflammation, regeneration and/or fibrosis following injury. However, elucidation of the specific roles of monocytes and macrophages has proven challenging, in part due to the tremendous plasticity and functional diversity of these cells, which are influenced by numerous factors, including the origin of the cells, the site of injury, the phase of injury and the aetiology of the disease[7].

For example, recent work using CD11b-diphtheria toxin receptor transgenic mice, with deletion of CD11b-expressing cells, demonstrated that $CD11b^+F4/80^+LY6C^+$ inflammatory macrophages are necessary to maintain fibrosis through the continued recruitment and activation of effector T_H2 cells within the lung and that depletion of macrophages reduced fibrosis and inflammation by reducing the number of T_H2 cells within the tissue[157]. By contrast, studies investigating the specific contribution of tissue-resident IL-4- and IL-13-activated macrophages suggested that these cells were anti-fibrotic, as mice with a tissue macrophage-specific deletion of IL-4Rα displayed increased inflammation but little change in hepatic fibrosis following infection with *S. mansoni*. The authors concluded that IL-4Rα-expressing macrophages may reduce inflammation and fibrosis by competing with T cells and possibly myofibroblasts for essential metabolites like L-arginine[145,158]. However, it is important to note that these studies were carried out in the liver, and subsequent studies investigating this phenomenon in the asthmatic lung failed to find a pathogenic or protective role for arginase-expressing myeloid cells, suggesting organ- or aetiology-specific differences in the role of these cells[159].

Macrophage and monocyte ontogeny can also affect the role of these cells in regulating disease. For example, a novel population of atypical monocytes derived from granulocyte and macrophage progenitors was recently reported to be critical for bleomycin-induced lung fibrosis. These atypical $CEACAM1^+MSR1^+LY6C^-F4/80^-CD11b^+$ cells, which were termed 'segregated-nucleus-containing atypical monocytes', were a critical source of tumour necrosis factor (TNF), and their depletion prevented bleomycin-induced fibrosis[160]. Studies using *Il4ra*$^{-/Flox}$*Lyz2*^{cre} transgenic mice, in which IL-4Rα is deleted in tissue-resident macrophages (which are $LysM^{hi}$), but not in newly recruited monocytes (which are $LysM^{low}$), revealed an important difference between recruited and tissue-resident monocytes and macrophages in regulating the pathogenesis of *S. mansoni*-induced fibrosis. IL-4Rα$^+$ tissue-resident macrophages suppressed inflammation in the tissue, whereas recruited $LysM^{low}$ monocytes were shown to slow the progression of type 2 cytokine-driven fibrosis[161].

Monocytes and macrophages can also directly influence fibrogenesis through substrate and matrix interactions. During macrophage polarization, the way in which macrophages utilize L-arginine changes drastically. Interferon γ (IFNγ)-activated macrophages activate inducible nitric oxide synthase to produce nitric oxide and citrulline, whereas IL-4- and IL-13-activated macrophages utilize arginase to produce ornithine, polyamines and proline, the last of which is a critical building block of collagen (as reviewed previously[162]). Thus, competition for L-arginine can directly influence the progression of fibrosis by limiting the substrates available for collagen synthesis. Conversely, macrophage-secreted matrix metalloproteinases (MMPs) regulate the progression and resolution of fibrosis by controlling matrix degradation and by regulating local inflammation

via facilitation of both extravasation and recruitment of inflammatory cells[163]. MMP12 is produced by IL-4- and IL-13-activated macrophages and can suppress the expression of the collagenolytic proteins MMP2, MMP9 and MMP13, resulting in diminished matrix degradation and augmented fibrotic responses following infection[164]. It has also been noted that macrophages are a key source of factors that regulate fibroblast growth, differentiation and survival, such as TGFβ, PDGF and several members of the fibroblast growth factor family[7,155,156]. During skin repair, resistin-like α (RELMα) secreted from IL-4- and IL-13-activated macrophages activates fibroblasts, which upregulate lysyl hydroxylase 2, a protein that regulates the mechanical crosslinking of collagen fibrils[165]. Other studies have shown that RELMα secreted from IL-4- and IL-13-activated macrophages is also critical in modulating type 2 cytokine production[166,167].

Finally, two recent studies have suggested that IL-4 and IL-13 may not be sufficient for the activation of tissue repair macrophages and that engagement of local tissue signals is also required[168,169]. Additionally, several recent studies have identified that IL-33 signalling may be important for the developmental remodelling by IL-4- and IL-13-activated macrophages that occurs in adipose tissues and the lung[170,171]. It is interesting to speculate that age-, tissue- and injury-specific co-signals may account for some of the differences in macrophage function observed across different organs and various aetiologies of disease. Together, these examples illustrate the diverse and multifaceted functional roles of monocytes and macrophages in both driving and regulating inflammation, tissue repair and fibrosis (FIG. 3).

Role of eosinophils in type 2 fibrosis. Eosinophils are considered to be potent drivers of inflammatory damage, and they secrete type 2 cytokines and TGFβ1 (REFS 172,173) in addition to many highly reactive enzyme-containing granules. Indeed, early studies in *Il5*$^{-/-}$ mice suggested a prominent role for eosinophils in the development of type 2 fibrosis in the liver[174]. In these experiments, *Il5*$^{-/-}$ mice infected with *S. mansoni* had a 40% reduction in fibrosis, and this was associated with reduced levels of IL-13. As expected, liver granulomas were almost completely devoid of eosinophils. However, it is important to note that these mice had developmental defects, including a lack of CD5^{+} B cells, that may have contributed to the observed phenotype[175]. Subsequent studies using ΔdblGATA mice and TgPHIL mice, which are also deficient in eosinophils, found that these mice display little to no defect in type 2 cytokine production, granulomatous inflammation or fibrosis following infection, thus calling into question the overall importance of eosinophils in fibrosis[176]. Nevertheless, therapeutic anti-IL-5 antibodies, such as mepolizumab, have demonstrated moderate success in ameliorating disease in human hypereosinophilic syndromes as well as in eosinophilic asthma[177,178]. Studies have also suggested that IL-5 may have an important role in type 2 fibrosis beyond the simple activation and recruitment of eosinophils. Still, other studies have demonstrated that the role of eosinophils in some fibrotic disorders can be quickly compensated for by other cells, including ILC2s, basophils, mast cells, NK cells and natural killer T cells.

Eosinophils have also been linked to the development of lung and skin fibrosis in chronic asthma and atopic dermatitis as well as vascular injury following high-dose irradiation, with various eosinophil granule proteins and pro-fibrotic cytokines playing key roles[28,179–182]. Distinct tissue-resident and recruited inflammatory eosinophil subsets with unique functional roles in T_H2 cell-driven allergic inflammation were also recently described[183]. Consequently, it is interesting to speculate that the recruited eosinophil subset could be the key inflammatory population driving the development of T_H2 cell-dependent fibrosis. Alternatively, decreases in the regulatory tissue-resident eosinophil population could augment type 2-mediated inflammation and exacerbate pulmonary fibrosis in the lung[183].

We recently showed elevated expression of the type 2 cytokines IL-4, IL-5 and IL-13 in murine models of non-alcoholic fatty liver disease (NAFLD) and additionally observed that serum levels of IL-4, IL-5 and IL-13 are highly correlated with METAVIR fibrosis scores in human patients with NAFLD or NASH, suggesting a role for type 2 immunity in the progression of NASH-associated liver fibrosis[184], which is quickly becoming the number-one indication for liver transplantation in the developed world. The presence of eosinophil-related gene signatures in liver biopsy samples could be used to distinguish patients with benign steatosis from those with inflammatory NASH. Additionally, eosinophils were observed near steatotic and fibrotic regions in both mice and humans; however, more work is needed to clarify whether these cells contribute to the pathogenesis of liver fibrosis.

To this point, eosinophils were also recently linked to tissue regeneration following injury to the liver or skeletal muscle. Indeed, a recent study found that eosinophils regulated liver regeneration following carbon tetrachloride intoxication and two-thirds partial hepatectomy by secreting IL-4 and IL-13, which act as hepatocyte mitogens in an IL-4Rα-dependent manner[185]. Similar findings were also reported in the case of skeletal muscle injury. However, in this case, eosinophil-derived IL-4 targeted the regenerative functions of muscle-resident fibrocyte and adipocyte progenitor cells that support myogenesis[186]. Thus, while the function of eosinophils in pathogenic fibrosis is somewhat variable, these cells clearly play important roles in tissue homeostasis following injury and may preferentially promote tissue regeneration in some settings (FIG. 3).

Role of fibroblasts in type 2 fibrosis. In contrast to the complex roles of many of the cell types discussed thus far, fibroblasts inarguably play a critical role in normal wound healing and the pathogenesis of fibrosis through the direct deposition of extracellular matrix in response to a diverse set of cytokines and growth factors (as recently reviewed[187]). Fibroblasts also serve as a vital source of cytokines, growth factors and chemotactic factors that influence the local microenvironment and

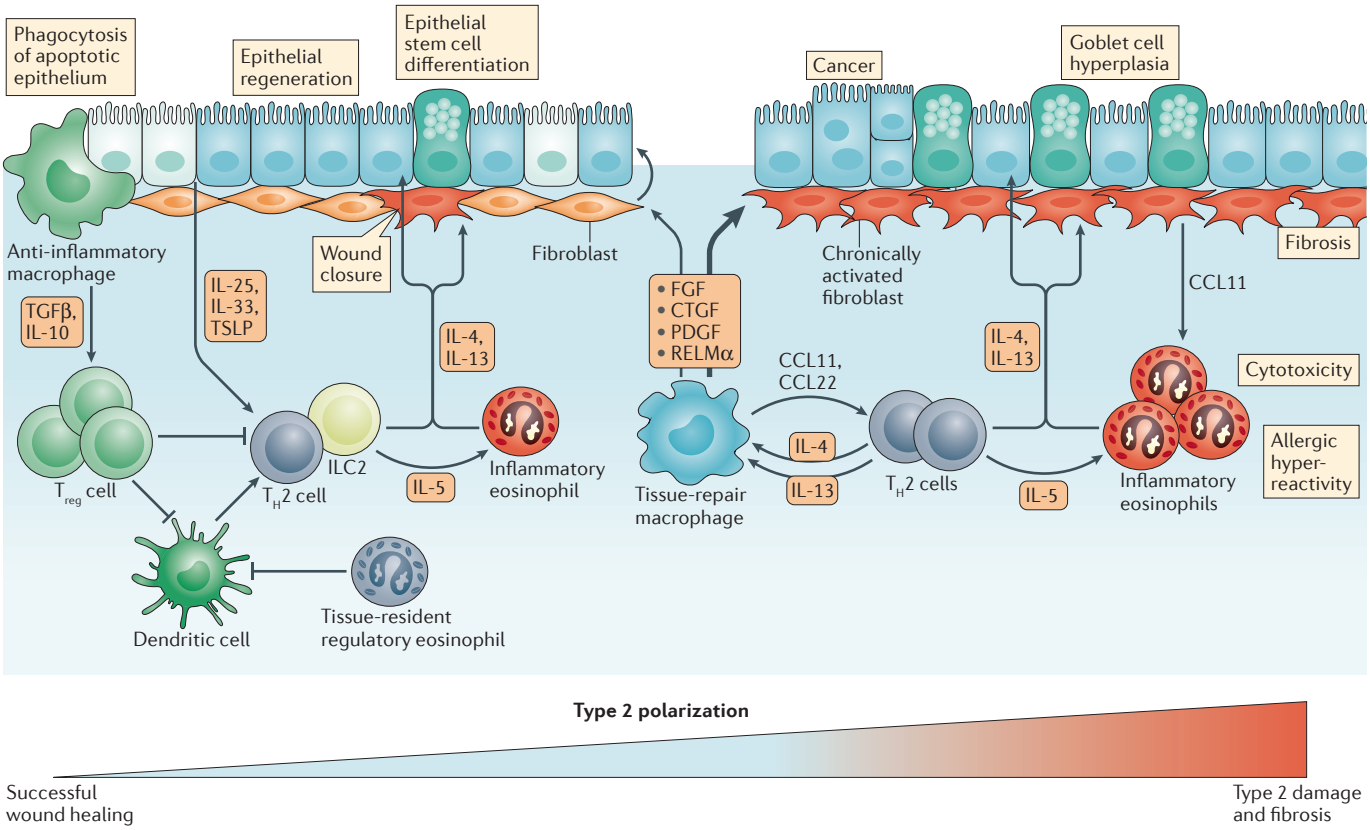

Figure 3 | **Role of accessory cells in wound repair and type 2 fibrosis.** Accessory cells, including macrophages, eosinophils, fibroblasts and epithelial cells, determine whether type 2 responses result in successful wound healing and tissue regeneration or progressive fibrosis and tissue pathology. In response to IL-4 and IL-13 signalling, epithelial cells proliferate and restore barrier function following injury. These cytokines also promote epithelial stem cell differentiation into various specialized cell types, including tuft cells and mucus-secreting goblet cells. In the case of highly polarized and chronic type 2 immune responses, biased differentiation and over-proliferation can result in goblet cell hyperplasia and excess mucus production in addition to predisposing individuals to cancers. Damaged epithelial cells also secrete alarmins, which can augment the type 2 response by increasing the expression of type 2 effector cytokines such as IL-4, IL-5 and IL-13. Eotaxins, such as CC-chemokine ligand 11 (CCL11), which are secreted from epithelial cells and fibroblasts in response to IL-13 signalling, recruit eosinophils. These eosinophils can augment epithelial regeneration by supplying a local source of IL-4 that triggers epithelial cells and other parenchymal cells to proliferate. Some populations of resident eosinophils can also dampen excessive type 2 responses by blocking antigen presentation and activation of T helper 2 (T_H2) cells. Nevertheless, in highly polarized responses, excessive inflammatory eosinophilia can result in cytotoxicity, allergic hyperreactivity and fibrosis. In direct response to IL-4 and IL-13, fibroblasts secrete collagens and adopt contractile phenotypes, which can aid in wound closure. Furthermore, growth factors such as amphiregulin can aid in re-epithelialization of the wound surface. However, excessive and repetitive type 2 signalling in fibroblasts results in the excessive deposition of extracellular matrix, ultimately leading to scarring and fibrosis. Throughout this process, macrophages play a key regulatory role by either augmenting or suppressing the type 2 response at various stages. Tissue repair macrophages provide key growth factors, which both aid in wound repair and promote fibrogenesis. Furthermore, these cells can recruit T_H2 effector cells, which further polarize the response. Anti-inflammatory macrophages can dampen this response by providing IL-10 and transforming growth factor β (TGFβ), which promote regulatory T cell differentiation. Overall, the type 2 response is complex, targeting many cell types and having both beneficial and pathogenic features that are not mutually exclusive. During the development of therapeutics, how agonism or antagonism of various aspects of this response will affect the system as a whole will need to be carefully considered. CTGF, connective tissue growth factor; FGF, fibroblast growth factor; ILC2, group 2 innate lymphoid cell; PDGF, platelet-derived growth factor; RELMα, resistin-like α; T_{reg}, regulatory T; TSLP, thymic stromal lymphopoietin.

the pathogenesis of fibrosis. It was recently shown that hepatic stellate cells (resident liver fibroblasts) are able to recruit eosinophils through the upregulation of CCL11 (also known as eotaxin) in response to IL-13 signalling[188]. Additionally, proliferating and migrating fibroblasts can activate pro-TGFβ through $\alpha_v\beta_6$ integrin and other integrin interactions that result in the generation of active TGFβ[189]. This pathway is critical in the pathogenesis of several models of hepatic, renal and pulmonary fibrosis[190,191]. However, it remains unclear whether integrin-mediated TGFβ activation plays a pathogenic pro-fibrotic role or a protective immunomodulatory role in highly polarized type 2 diseases; therefore, further studies are warranted.

Surprisingly, recent work confirmed that IL-4 and/or IL-13 signalling directly through fibroblasts is necessary for the development of hepatic fibrosis during a highly polarized type 2 inflammatory response. *Pdgfrb*^{cre}*Il4ra*$^{Flox/Flox}$ mice, which have fibroblasts deficient in IL-4Rα, failed to develop fibrosis in response to IL-13 (REF. 188). Because there was no decrease in the number of IL-4- and IL-13-activated macrophages in these studies, the authors also questioned the importance of pro-fibrotic IL-4- and IL-13-activated macrophages and intermediate factors such as TGFβ during highly polarized type 2 immune responses. Alternatively, the authors suggested that the pro-fibrotic functions of IL-4- and IL-13-activated macrophages are partially dependent on the prior activation of IL-4Rα-expressing fibroblasts by IL-4 or IL-13. They also implied that strategies incorporating cell-specific blockade of IL-4 or IL-13 signalling may prevent fibroblast-driven pathological fibrosis while maintaining the pro-regenerative and anti-inflammatory functions of type 2 immunity (FIG. 3).

Role of epithelial cells and other cell types. As mentioned above, the epithelia of the airways, gastrointestinal tract and liver are initiators of type 2 immunity via the secretion of alarmins. In contrast to alarmin expression, epithelial expression of chitin-degrading enzymes, including acidic mammalian chitinase (AMCase) and chitotriosidase 1 (CHIT1), has yielded mixed results. Early studies identified elevated levels of AMCase in the epithelial cells and macrophages of mice following allergen exposure and in humans with asthma[192–194]. Blockade of AMCase with anti-AMCase sera or allosamidin inhibited ovalbumin (OVA)-induced airway inflammation and IL-13 secretion in mice, suggesting that AMCase was required for allergen-induced airway inflammation[193]. Although administration of chitin can induce allergic responses that can be prevented by administration of AMCase[195,196], Fitz and colleagues did not find any apparent role for AMCase in controlling the severity of allergic airway disease using HDM-, OVA- or cockroach allergen-induced airway inflammation in combination with either a small-molecule inhibitor targeting AMCase or AMCase deficiency in mice[197]. Nevertheless, AMCase-deficient mice exhibited impaired type 2 responses with a concomitant increase in neutrophilia and lymphocytic infiltration that compensated for the lack of type 2 effector function. In agreement with these studies, we observed an initial defect in type 2 effector functions during acute HDM challenge but found no significant impact on the progression of disease during chronic HDM exposure[198]. By contrast, we observed a profound impact on type 2 immune responses in the gastrointestinal tract in AMCase-deficient mice following intestinal helminth infection. Interestingly, these effects seemed to be most prominent in older mice[199]. A recent study also suggested that impaired clearance of chitin might contribute to the persistent activation of type 2-associated fibrogenic pathways in the lungs of aged mice and humans with interstitial lung diseases that exhibit epithelial cell dysfunction and reduced AMCase activity, but not CHIT1 activity[199]. It therefore appears that in response to chitin-rich microorganisms or allergens, potent type 2 immune responses can be invoked, in which chitinases may regulate the degree of inflammation. It remains undetermined to what degree AMCase and CHIT1 contribute to common allergen-driven inflammation.

In addition to AMCase and the alarmins, epithelial cell-derived TGFβ1 is a surprising but important type 2-promoting growth factor whose expression is elicited by IL-33 (REF. 200). Following exposure to allergens from *Alternaria* fungi, TGFβR2-expressing ILC2s were recruited to TGFβ1-secreting epithelial cells, forming early innate inflammatory foci and propagating type 2-mediated airway inflammation and airway hyperreactivity. Local epithelial cell-derived TGFβ1 can also contribute to subepithelial fibroblast activation and airway remodelling[201], placing epithelial cell-derived TGFβ1 and ILC2-derived IL-13 in an innate inflammatory and fibrotic loop. A recent study by Van Dyken and colleagues showed that tissue-derived signals, including the alarmins, provide a critical tissue-derived checkpoint, limiting the terminal differentiation and activation of both T_H2 cells and ILC2s[134]. In line with previous studies[115], inhibition of all three alarmins was required to dampen T_H2 cell-mediated tissue inflammation[134].

In addition to being a key source of important type 2-initiating cytokines, epithelial cells can respond to IL-4 and IL-13 directly, inducing important type 2 functions such as mucus secretion[202]. It was also recently shown that epithelial cells expressing IL-4Rα proliferate in response to IL-4 and IL-13 and, furthermore, that IL-4 and IL-13 contribute to the proliferation and differentiation of adult tissue stem and progenitor cells. Using *Krt19*^{CreERT}*Il4ra*$^{Flox/Flox}$ mice, we recently demonstrated that biliary proliferation, which accompanies fibrosis during schistosomiasis or during experimental fibrosis induced by IL-13 overexpression, is completely abolished when epithelial cells lack IL-4Rα[188]. We also observed the biased differentiation of hepatic progenitor cells towards a cholangiocyte fate in response to IL-4 or IL-13 stimulation. Similarly, several groups have elucidated feedforward loops in the gut involving epithelial-derived IL-25 inducing IL-13 production by ILC2s, with IL-13 subsequently signalling through LGR5$^+$ intestinal stem cells and/or their progeny. In response, these cells proliferate and exhibit differentiation biased towards tuft and goblet cell fates, enhancing parasite detection and expulsion[83–85]. Others have shown that fibroblast-derived IL-33 can directly target these stem cells and enhance barrier immunity against *Salmonella* infection[203]. Whether this ILC2–tuft cell feedforward loop also operates in the lung or any other organ is unclear. Nevertheless, these examples illustrate that type 2 signalling through the epithelium and epithelial stem cells plays important roles in epithelial regeneration and the maintenance of barrier function during the course of injury. When designing therapies that aim to block the fibroproliferative effects of type 2 signalling through systemic cytokine or receptor blockade, the potential adverse effects that could result due to impaired epithelial regeneration and function should be considered (FIG. 3).

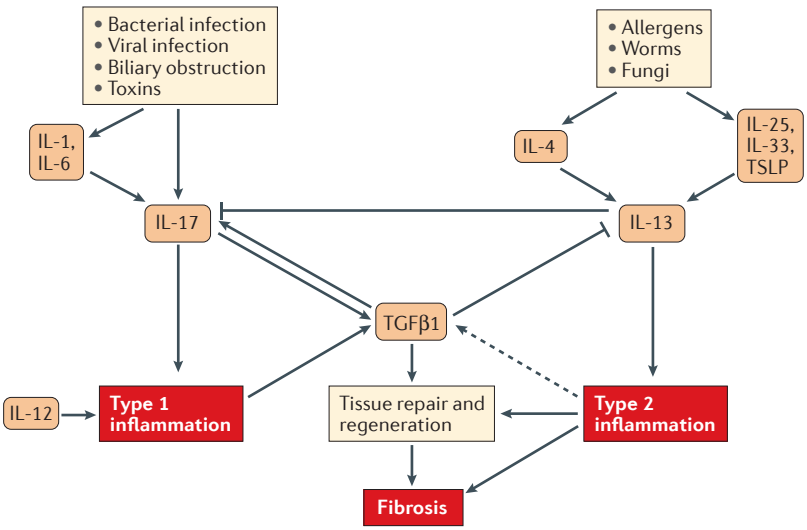

Figure 4 | **Crosstalk between core immunological pathways of fibrosis.** Two key immunological mechanisms driving tissue repair and fibrosis have been described, and both pathways exhibit cross-regulatory activity. Bacterial and viral infections as well as toxic substances like bleomycin and carbon tetrachloride have been shown to activate the IL-1–IL-17–transforming growth factor β (TGFβ) axis, which is believed to be a major driver of tissue repair and fibrosis during sustained type 1- and T helper 17 cell-driven inflammatory responses. TGFβ has feedback anti-inflammatory activity and simultaneously activates extracellular matrix production by myofibroblasts. IL-13, by contrast, has been identified as the major driver of tissue repair and fibrosis during sustained type 2 responses induced by allergens, worms and some fungi. The two pathways also exhibit substantial negative regulatory activity, as depicted in the figure. TSLP, thymic stromal lymphopoietin.

Cross-regulation of fibrotic pathways

Type 2 immunity is tightly regulated by several distinct mechanisms (as recently reviewed[4]), which help to prevent complications resulting from sustained type 2 signalling. A number of type 1-associated cytokines are potent inhibitors of type 2 immunity through their effects on naive $CD4^+$ T cell differentiation. In particular, IL-12 signalling prohibits the differentiation of the T_H2 cell lineage by promoting the differentiation of naive T cells towards a T_H1 cell phenotype. IFNγ-activated macrophages upregulate IL-12 and suppress IL-10 expression, further shifting naive helper T cells towards a T_H1 or T_H17 cell fate[204–207]. IL-10 and TGFβ produced by DCs and regulatory T cells can also actively suppress both type 1 and type 2 responses, thereby inhibiting excessive cytokine production[208,209].

Additionally, the T_H2 effector cytokine IL-13 engages an inducible, high-affinity decoy receptor, IL-13Rα2, which suppresses IL-13 effector function by sequestering the protein away from the IL-4Rα–IL-13Rα1 signalling receptor complex[210,211]. Interestingly, these suppressive mechanisms have functional redundancy and work in collaboration to control excessive type 2 immunity[212]. Recent studies demonstrated that several type 1- and T_H17-derived cytokines can drive the production of IL-13Rα2, suggesting potent cross-regulation of IL-13 effector function by type 1- and T_H17-driven immunity. Indeed, it has been shown that several cytokine combinations, including TNF and IL-4 or IL-17, can synergize to drive high levels of IL-13Rα2 expression, blocking the ability of IL-13 to upregulate downstream targets such as CCL26 in both human and mouse fibroblasts[213].

In addition to the primary role of IL-13Rα2 as a decoy receptor for IL-13, Elias and colleagues have reported that chitinase-3-like protein 1 (CHI3L1) may signal through IL-13Rα2 (REF. 214). Recently, a binding partner of the CHI3L1–IL-13Rα2 complex, called insulin-like growth factor-binding protein 3 receptor (IGFBP3R, also known as TMEM219), was identified. It has been suggested that IGFBP3R regulates the signalling properties of the CHI3L1–IL-13Rα2 complex and augments the decoy functions of IL-13Rα2 in addition to controlling diverse pathways regulating TGFβ1 production, antibacterial responses, inflammasome activation, oxidant injury and apoptosis[215]. Nevertheless, independent validation and replication of these studies are necessary.

Regulation of programmed cell death, whether apoptosis, necroptosis or pyroptosis, may be an additional core pathway modulating remodelling and fibrotic responses. Whether too much or too little, the rate and relevance of cell death with respect to disease initiation and progression continue to be debated. Damage to or induced senescence of alveolar type 2 cells is considered to be one of the earliest pathological events in IPF[216,217], and it has been suggested that senescence may be linked to low-level ongoing inflammation and thus may be a key initiator of fibrosis (as recently reviewed[218]). Indeed, experimental administration of an anti-Fas antibody[219] or bleomycin[220], which cause epithelial cell damage, apoptosis and cell death, is frequently used as a model of pulmonary fibrosis; this finding implicates epithelial cell impairment, including both senescence and cell death, in the pathogenesis of pulmonary fibrosis. In addition, fibroblasts isolated from patients with IPF appear to have a slower growth rate along with increased activation and release of pro-fibrotic mediators yet show increased rates of apoptosis[221]. In regions of epithelial cell death, increases in myofibroblast activation have been observed, presumably for repair of the damaged epithelium[222]. Similarly, apoptosis of endothelial cells with the release of CTGF can also contribute to fibrogenesis[223], suggesting that local tissue damage and pervasive cell death may be important drivers of fibrosis. In response to such tissue damage and apoptosis, both inflammatory[224] and anti-inflammatory pathways have been identified, with increased secondary apoptosis[224] reducing tissue build-up[225,226]. In particular, the phagocytosis of apoptotic epithelial cells, either by neighbouring epithelial cells[87,227] or by professional phagocytes[228,229], activates distinct anti-inflammatory responses that limit intestinal and airway inflammation. Additionally, engagement of apoptotic cell sensors may be a co-requisite, along with IL-4 and IL-13 signalling, to fully potentiating the activation of tissue repair macrophages[168]. Together, these data suggest that cell death may be a core fibrotic pathway, both propagating disease through mediator release and resolving local tissue damage by regulating inflammation and thus reflecting the cyclic paradigm of wound healing that may lead to fibrosis when chronically activated or dysregulated (FIG. 4).

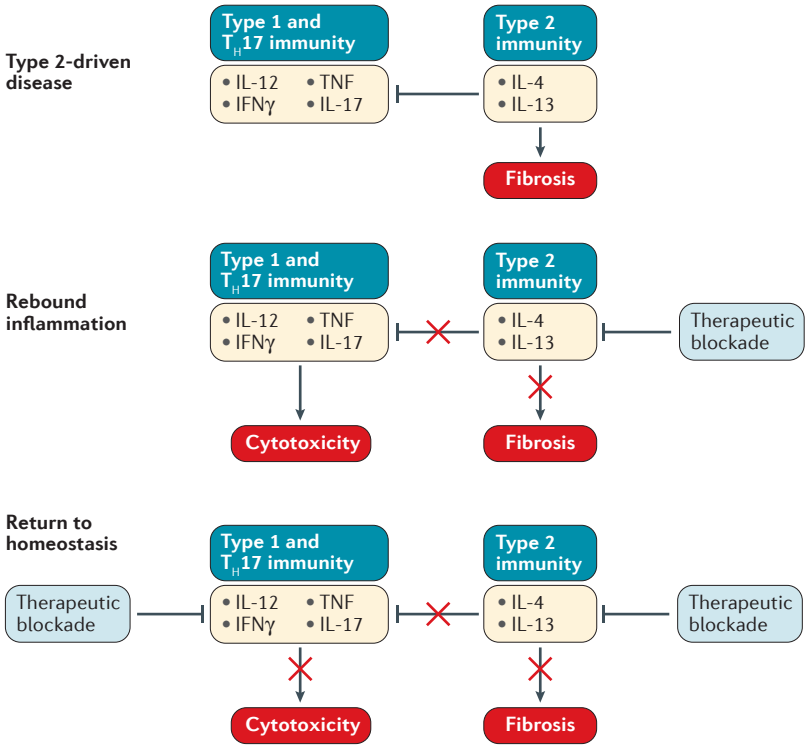

Figure 5 | **Rebound inflammation during therapeutic intervention.** Following therapeutic blockade of type 2 immunity, important cross-regulatory networks are dysregulated, allowing type 1- and/or T helper 17 (T_H17) cell-driven inflammation to rebound and exposing subjects to potentially harmful cytotoxic side effects. Successful therapeutics should return patients to a healthy homeostatic set point, perhaps by simultaneously targeting the pathogenic actions of sustained type 1- and/or T_H17-driven and type 2 inflammation. IFNγ, interferon γ; TNF, tumour necrosis factor.

Future directions and opportunities

Given the extensive evidence demonstrating the pro-fibrotic nature of type 2 immunity and, in particular, IL-4 and IL-13 signalling when continuously activated, this type of immune response has proven attractive for therapeutic modulation during the course of various allergic and fibrotic diseases. Several groups have investigated or are actively investigating blockade using antibodies and/or antagonists targeting various aspects of the IL-4 and IL-13 signalling pathways alone or in combination using bifunctional or bi-specific strategies. The results of such trials in various diseases have been mixed, and in some cases, the trials have demonstrated worsened outcomes in patients receiving treatment compared with control arms[74,79,80].

As stated earlier, several type 1 cytokines have been shown to counter-regulate type 2 immunity. However, type 2 cytokines are also important regulators of type 1- and T_H17-driven inflammatory responses. Recently, several studies have revealed that blockade of type 2 cytokines can dysregulate this cross-regulatory mechanism and promote type 1- and T_H17-driven inflammation, exacerbating IFNγ- and IL-17A-driven cytotoxic injury. During the course of experimental murine schistosomiasis and in pulmonary granuloma models, blocking IL-13 alone significantly reduces fibrosis but concurrently leads to increases in IFNγ production and subsequent increases in TNF production and inflammatory tissue necrosis, exacerbating liver and lung damage. However, dual blockade of IL-13 and IFNγ led to a marked reduction in fibrosis and eliminated the rebound type 1 inflammation and associated damage observed in mice treated with anti-IL-13 alone[230]. Similarly, it has been shown that blockade of IL-4 and/or IL-13 in HDM-induced allergy models induces substantial T_H17 cell-driven neutrophilic inflammation; however, dual blockade of IL-13 and IL-17A protected mice from both eosinophilic and neutrophilic inflammation and eliminated associated mucus production and airway hyperreactivity, illustrating the benefits of dual- or multi-blockade strategies to combat rebound inflammation[230,231] (FIG. 5). It is interesting to speculate that some of the disappointing outcomes observed in clinical trials blocking aspects of the IL-4 and/or IL-13 signalling pathways may be the result of unintended dysregulation of the type 1- and T_H17-driven inflammatory responses and/or disruption of important beneficial aspects of IL-4 and IL-13 signalling, such as epithelial regeneration. Together, these studies suggest that careful targeting and dosing of therapeutics will be necessary to successfully block the pathogenic features of sustained type 2-driven inflammation without sacrificing the beneficial features of wound repair and epithelial regeneration or subjecting patients to potentially harmful rebound inflammatory responses. Uncovering the various cellular, molecular and genetic mechanisms that sustain pro-fibrotic signalling and inhibit endogenous mechanisms to end wound healing responses will be an important research goal in the coming years.

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Acknowledgements
This work was supported by the Intramural Research Program of the US National Institutes of Health National Institute of Allergy and Infectious Diseases.

Competing interests statement
The authors declare no competing interests.

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doi:10.1038/nri.2017.150

REPLY Response to Orlova *et al*. "Science not art: statistically sound methods for identifying subsets in multi-dimensional flow and mass cytometry data sets"

Yvan Saeys, Sofie Van Gassen and Bart Lambrecht

doi:10.1038/nri.2017.151

This correspondence relates to the article:

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Nat. Rev. Immunol. **16**, 449–462 2016